Remarks

Prior to entry of the foregoing amendment, claims 1-9 and 22-31 were pending in this application and were rejected on various grounds. Claims 1, 5, 22 and 23 have been amended, claims 2, and 28-31 have been canceled. Support for these amendments is found at least at page 14, lines 15-20, page 38, lines 35-36, and page 43, line 27. The amendments do not add new matter.

All amendments and cancellations are made without prejudice. Applicants specifically reserve the right to pursue any canceled subject matter in one or more continuing applications.

Arguments

Applicants note the withdrawal of earlier rejections of clam 1-9 and 22-28, 30 and 31 under 35 U.S.C. 102(e), and the provisional rejections of claims 1-9 and 22-31 under the judicially created doctrine of obviousness type double patenting.

Claim Rejections Maintained

1. Claims 5 and 23 remained rejected under 35 U.S.C. 112, first paragraph for allegedly failing to comply with the written description requirement. According to the rejection, the recitation "monoclonal antibody 2C4 (ATCC HB12679) or a humanized form thereof" reads on a genus of antibodies defined only by the function that the humanized antibodies within the genus bind ErbB2 and block ligand activation of an ErbB receptor, "for which the description is not representative." In particular, the Examiner asserts that the definition covers humanized 2C4 antibodies which only possess one or two of the CDR residues of monoclonal antibody 2C4.

Without acquiescing to the rejection, or the reasoning underlying the rejection, claims 5 and 23 have been amended to recite that the claimed humanized antibodies bind to the same epitope as monoclonal antibody 2C4 (ATCC HB12697), which is believed to obviate their rejection.

2. Claims 1-9 and 22-31 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Huzdiak (U.S. Patent No. 5,725,856) and Ross II (U.S. Patent

No. 5,994,071), in view of Sliwkowski (J. Biol. Chem. 269:14661-14665, 1994) or Klapper (Oncogene, 14:2099-2109, 1997), and further in view of Plowman (U.S. Paten No. 5,804,396) or Akita (U.S. Patent No. 5,968,511) or Greene (U.S. Patent No. 6,417,168) "for reasons of record." In addressing Applicants' earlier arguments, the Examiner notes that the fact that monoclonal antibody 2C4 is more effective than huMab4D5-8 in blocking ligand activation of an ErbB receptor "is not the only motivation for using 2C4 in the claimed methods." According to the Examiner, "[b]ecause the prior art recognized that prevention of ErbB2 oligomerization induced by ligands such as heregulin was a therapeutic target for the treatment of cancer, it would have been prima facie obvious to one or ordinary skill in the art at the time the invention was made to have used monoclonal antibody 2C4 of Sliwkowski because Sliwkowski teaches that monoclonal antibody has this function." In addition, the Examiner finds that "the monoclonal antibodies of Klapper would also have been useful for the purpose of treating prostate cancer through the inhibition of heregulin activation of ErbB receptors." Huzdiak and Ross II were cited for their teaching of general methods for treatment of prostate cancer using antibodies that bind ErbB2. Although the Examiner acknowledges that these references do not teach the use of antibodies inhibiting the formation of ErbB hetero-oligomers, she holds that such antibodies were known in the art (Sliwkowski), and Plowman, Akita and Greene recognized that the inhibition of ErbB2 oligomerization with other ErbB receptors is a therapeutic target for the treatment of cancer. From this the Examiner concludes that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the antibodies of Sliwkowski or Klapper in he method of Huzdiak to treat prostate cancer. According to the rejection, one would have been motivated to use antibodies that inhibited ligand activation of an ErbB receptor since the art recognized that ErbB2 was activated by the formation of heterodimers and that ErbB2 activation plays a role in the growth of prostate cancer cells.

Applicants submit that the presently claimed invention is patentable over the cited art.

The combination of Huzdiak or Ross II with the secondary references is improper

In the examples of the Hudziak patent (cols. 13-19), the breast tumor cells treated with the antibodies were selected based on HER2 overexpression, rather than by a mechanism based on ligand-activated HER2 hetero-oligomer formation. Indeed, the preferred antibody in Hudziak *et al.*, the 4D5 antibody, is specifically excluded by the claims herein, since that antibody does not block ligand activation of an ErbB receptor substantially more effectively than humanized monoclonal antibody huMAb4D5-8 (HERCEPTIN®), and

does not block by 50% or greater binding of monoclonal antibody 2C4 (ATCC HB12697) to ErbB2. Similarly, Ross II teaches cancer overexpressing HER2, not cancer characterized by ligand activated HER2 hetero-oligomer formation. The secondary references, on the other hand, concern tumor cells characterized by heterodimer formation. Combining of Huzdiak or Ross II with a secondary references discussing tumors characterized by ligand-activated formation of HER2 hetero-oligomers, such as Sliwkowski, Akita, or Greene is impermissible under patent law which prohibits combining unrelated teachings, such as these.

The claimed invention involves unexpected results

It is well established that unexpected results, including both unexpected differences in degree and kind, should be considered as evidence of non-obviousness. See, *e.g.*, In re Chupp, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987), where the court stated: ""Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness." In particular, the presence of an unexpected property is evidence of non-obviousness. See, *e.g.*, In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963), and Ex parte Thumm, 132 USPQ 66 (Bd. App. 1961).

The claims herein concern therapy of "androgen independent" prostate cancer. Successful treatment of that form of prostate cancer was highly unexpected at the time the invention was made. In particular, as shown in Examples 5 and 6, whereas Herceptin® alone had little or no clinical activity in androgen dependent tumor models, MAb 2C4 (which blocks ligand activation of ErbB2/HER2 more effectively than Herceptin®) had activity in the models (page 53, line 35). This was unexpected from the prior art, which taught 4D5 or Herceptin® as the preferred antibody for cancer therapy.

In view of such unexpected results, a holding of non-obviousness would be in order.

The cited combination of references does not make obvious the claimed invention

Even if the cited references could be properly combined, they would still not make obvious the invention claimed in the present application.

The primary references, Hudziak and Ross II are discussed above. They do not refer to therapy of androgen independent prostate cancer. Nor do they disclose that antibodies could be developed that not only treat androgen independent prostate cancer but further block ligand activation of an ErbB receptor substantially more effectively than humanized monoclonal antibody huMAb4D5-8 (HERCEPTIN®), or block by 50% or greater binding of monoclonal antibody 2C4 (ATCC HB12697) to ErbB2. Indeed, the preferred antibody in

Hudziak is antibody 4D5, which is not expected to block ligand activation of an ErbB receptor more effectively than its humanized version.

Applicants submit that the secondary references or general knowledge in the art did not provide a reasonable expectation that the antibodies of Sliwkowski et al. or Klapper et al. could be successfully used to treat prostate cancer, especially androgen independent prostate cancer, or that antibodies that block ligand activation of an ErbB receptor substantially more effectively than HERCEPTIN® could be successfully made and used to treat androgen independent prostate cancer.

While Sliwkowski et al. mentions murine MAb 2C4 (a humanized form of 2C4 is not described), its focus is on biochemical characterization of a HER2-HER3 complex, rather than guidance concerning therapy of human cancer, let alone androgen independent prostate cancer. Applicants submit that the skilled clinician would not consider Sliwkowski *et al.* to provide either the motivation or reasonable expectation of success for treating androgen independent prostate cancer.

In Klapper *et al.*, the *in vivo* studies were performed with gastric cancer cells selected due to HER2 overexpression (*e.g.* Fig. 1). Therapy of androgen independent prostate cancer is not taught, nor is therapy with an antibody that blocks by 50% or more binding of MAb 2C4, or therapy with humanized 2C4.

Plowman *et al.* concerns assaying a potential agent for activity in inhibition of signal transduction by a HER2/HER3, HER2/HER4 or HER3/HER4 heterodimer. Therapy of androgen independent prostate cancer is not disclosed or suggested, much less therapy with an antibody that locks binding of MAb 2C4, blocks ligand activation of an ErbB receptor more effectively than Herceptin®, or therapy with humanized 2C4.

Akita *et al.* concerns ErbB3 antibodies. The use of such antibodies to treat androgen-independent prostate cancer, or therapy of androgen independent prostate cancer with an antibody that blocks by 50% or more binding of MAb 2C4, blocks ligand activation of an ErbB receptor more effectively than Herceptin®, or therapy with humanized 2C4 is not disclosed or suggested.

Greene *et al.* in the '168 patent is interested in treating a p185-mediated tumor with a peptide that dimerizes with an ErbB protein and that is deficient in tyrosine kinase activity. Therapy of androgen independent prostate cancer with an antibody that blocks by 50% or more binding of MAb 2C4, blocks ligand activation of an ErbB receptor more effectively than Herceptin®, or therapy with humanized 2C4 is not disclosed or suggested in Greene.

Since the secondary references do not make up for the deficiencies of the primary references, and the combination of either Hudziak or Ross II with any or all of the secondary references does not create a reasonable expectation of treating androgen independent prostate cancer with antibodies that block ligand activation of an ErbB receptor more effectively than Herceptin®, and block by 50% or more binding of MAb 2C4, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

3. The provisional rejection of claims 1-9 and 22-31 under the judicially created doctrine of obviousness-type double patenting over claims 1, 2, 49, 16-22, 24-27, and 60-63 of copending application No. 09/602,812 was maintained "for reasons of record."

The rejection is respectfully traversed. In relevant part, copending application No. 09/602,812 claims the treatment of (1) EGFR and ErbB2 expressing cancer (claim 1 and claims dependent therefrom, as well as claim 62), (2) cancers that express but do not overexpress ErbB2 receptor (claim 27 and claims dependent thereon), and colon, rectal or colorectal cancer (claim 34). These methods do not make obvious the treatment of androgen independent prostate cancer, as claimed in the present application. The Examiner notes that a "preferred embodiment described in the specification [of Serial No. 09/602,812) is prostate cancer." Since the rejection is based on obviousness-type *double patenting*, one should look to the inventions claimed in the two applications. Anything that is disclosed but not claimed is irrelevant.

Whereas the claims of the present application are actually drawn to methods for treating *androgen independent prostate* cancer, the claims of application Serial No. 09/602,812 concern methods for treating cancer that expresses EGFR and ErbB2; colon, rectal and colorectal cancer, lung cancer (*e.g.* non-small cell lung cancer), cancer that expresses but does not overexpress ErbB2 receptor, or breast cancer (*e.g.* metastatic breast cancer). In a restriction requirement issued in Serial No. 09/602,812 on October 2, 2001 (Paper No. 7, page 5), the Office has previously held that therapy of different species of cancer are patentably distinct because "Different types of cancers have different mechanisms of action, and require distinct treatment protocols," This is especially true in the present case, where, as indicated above, therapy of androgen independent prostate cancer, associated with unexpected results, is treated. Accordingly, applicants respectfully request that the provisional obviousness-type double patenting rejection over application Serial No. 09/602,812 be reconsidered and withdrawn.

All claims pending in this application are believed to be in prima facie condition for allowance, and an issuance of a Notice of Allowance is respectfully solicited.

Sincerely,

Date: April 15, 2005

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